PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
RCS/PF4877		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/07612	11.07.2003	12.07.2002

International Patent Classification (IPC) or both national classification and IPC
A61K31/445

Applicant
GLAXO GROUP LIMITED et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27.01.2004	08.10.2004

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/07612

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-74 as originally filed

Claims, Numbers

1-18 received on 07.09.2004 with letter of 03.09.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1 (part)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1 (part) are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☒ the claims, or said claims Nos. 1 (part) are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1 (part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-18
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	

2. Citations and explanations

   see separate sheet

III. Non-establishment of opinion

In view of a lack of clarity and disclosure (Articles 5 and 6 PCT), claim 1 has only been searched insofar as the prodrugs are acetate, formate or benzoate derivatives of hydroxy, sulfhydryl or amine groups or ester derivatives of carboxylic acid groups. The following examination is performed for completely searched subject matter only.

V. Reasoned statement

Reference is made to the following documents:

D1: Bioorganic & Medicinal Chemistry Letters, 2000, 10(16), 1803-1806

D2: US-A-6048900

Novelty

Compound 3 of D1 differs from the present claims because the linker group corresponding to present group E is n-pentylene.

The general formula in claim 1 of D2 overlaps with present formula (I). However, the present claims may be considered a novel selection, in which R^5 is Ar^1-piperidyl-n-butylene and R^1 or R^2 is Ar_2-Ar_3, as such a sub-group is not disclosed in D2.

Claims 1-18 fulfil the requirements of Article 33(2) PCT.

Inventive step

The technical problem underlying the present application appears to be the provision of compounds useful in the treatment of hyperlipidemia. The compound of D1 is a weak chemokine receptor ligand. Those of D2 are useful in the treatment of obesity related disorders such as hyperlipidemia. D2 may therefore be taken as the closest prior art. Although the present compounds are formally encompassed by the general formula of D2, it would be clear to the skilled person that it is not credible that all compounds falling within the general formula (I) of D2 can have qualitatively equivalent activity - the general formula (I) is so broad it encompasses not only the polycylic compounds illustrated by the examples, but also simple acyclic compounds such as acetamide. The more specific teaching of D2, wherein the R^1-R^5 substituents have the preferred definitions given in col. 3, l. 20 to col. 4, l. 19 does not encompass the present compounds because of the meaning of the Ar_1 group. Therefore it would not be obvious to solve the above-formulated technical problem by providing the compounds according to claim 1. Thus those claimed compounds which have the alleged activity may be

considered inventive.

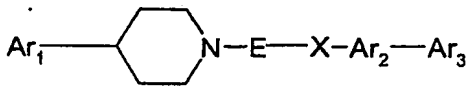
claims 1-18 fulfil the requirements of Article 33(3) PCT.

Industrial applicability

Claims 1-18 fulfil the requirements of Article 33(4) PCT.

Claims

1. A compound of formula (I), physiologically acceptable prodrugs, salts or solvates thereof;



(I)

wherein

Ar_1 is:

(i) phenyl, naphthyl or phenyl fused by a C_{3-8}cycloalkyl; or

(ii) heterocyclyl selected from the list consisting of: monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and wherein individual rings of said radicals may be independently saturated, partially unsaturated or aromatic, provided that at least one ring is aromatic;

where Ar_1 is optionally substituted by 1-4 R^1 groups which may be the same or different;

Ar_2 is a phenyl group, a 5-6 membered heteroaromatic group or a bicyclic heteroaromatic group, each of which is optionally substituted by 1-4 groups independently selected from the list: C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, C_{1-6}acyl, C_{1-6}acyloxy, amino, C_{1-4}alkylamino, di-C_{1-4}alkylamino, $-(CH_2)_nOH$, $-(CH_2)_nNR_xR_y$, $-O(CH_2)_nO(CH_2)_mOR^a$, $-O(CH_2)_nC(O)NR_xR_y$, $-O(CH_2)_nCN$, C_{2-5}alkenyl, $-O(CH_2)_nCO_2R^a$, $-OSO_2(CH_2)_pCH_3$, $-OSO_2NR_xR_y$ and $-CO_2(CH_2)_pCH_3$;

Ar_3 is:

(i) phenyl, naphthyl or phenyl fused by a C_{3-8}cycloalkyl; or

(ii) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and wherein individual rings of said radicals may be

independently saturated, partially unsaturated, or aromatic, providing that at least one ring is aromatic,

wherein Ar_3 is optionally substituted by 1-4 groups independently selected from the group consisting of: hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkenyloxy, C_{1-4}perfluoroalkoxy, C_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_3$, $-NHSO_2CH(CH_3)_2$), fluoroC_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_2CF_3$), C_{1-4}alkylcarbonylamino, fluoroC_{1-4}alkylcarbonylamino, halogen (such as chlorine), nitrile, nitro, C_{1-4}perfluoroalkyl, C_{1-4}alkylcarbonyl, fluoroC_{1-4}alkylcarbonyl, C_{1-4}alkoxycarbonyl, aminocarbonyl, C_{1-4}alkylaminocarbonyl, di-C_{1-4}alkylaminocarbonyl, C_{1-4}alkylsulfonyl, C_{1-4}alkylaminosulfonyl, di-C_{1-4}alkylaminosulfonyl, C_{1-4}alkylsulfonyl and C_{1-4}alkylsulfoxy;

E is n-butylene;

X is $-CONR^a-$ or $-NR^aCO-$ (where the left hand side of the linkage is attached to E);

wherein

R^1 is halogen, C_{1-4}alkoxy or C_{1-4}alkyl;

R^a is C_{1-4}alkyl or hydrogen;

R_x and R_y are independently hydrogen, C_{1-4}alkyl, hydroxy or C_{1-4}alkoxy, where R_x and R_y are not both hydroxy or both C_{1-4}alkoxy; or R_x and R_y together with the nitrogen to which they are attached form a 5-membered ring which ring is optionally substited by $-O(CH_2)_nC(O)NR_xR_y$, $-O(CH_2)_nCN$, $-O(CH_2)_nO(CH_2)_mOR^a$, $-O(CH_2)_nCO_2R^a$, $-OSO_2NR_xR_y$, $-OSO_2(CH_2)_pCH_3$, $-(CH_2)_nC(O)NR_xR_y$, $-(CH_2)_nCN$, $-(CH_2)_nO(CH_2)_mOR^a$, $-(CH_2)_nCO_2R^a$, $-(CH_2)_nC(O)R^a$, $-SO_2NR_xR_y$, $-SO_2(CH_2)_pCH_3$, $-CH=CHC(O)NR_xR_y$, $-CH=CHCN$, $-CH=CHCO_2R^a$, $-CO_2R^a$, $-C(O)R^a$, $-C(O)NR_xR_y$ and C_{2-5}alkenyl;

n and m are independently 1-4; and

p is 0-4.

2. A compound according to claim 1 wherein Ar_1 is phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indolyl, benzofuranyl, benzothiophenyl or indazolyl.

3. A compound according to claim 2 wherein Ar_1 is phenyl, 1,2,3,4-tetrahydronaphthyl or indolyl.

4. A compound according to any preceding claim wherein X is $-NR^aCO-$.

5. A compound according to any preceding claim wherein Ar_2 is phenyl, pyridyl, thiazolyl, oxazolyl, pyrazolyl or imidazolyl.

6. A compound according to claim 5 wherein Ar_2 is optionally substituted by one or two substituents independently selected from the list: C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, aminoC_{1-4}alkyl, mono-C_{1-4}alkylaminoC_{1-4}alkyl, di-C_{1-4}alkylaminoC_{1-4}alkyl, $-O(CH_2)_nC(O)NR_xR_y$ (where R_x and R_y are independently hydrogen or C_{1-4}alkyl and n is 1-3) or $-CO_2(CH_2)_pCH_3$ (where p is 0-3).

7. compound according to any preceding claim wherein Ar_3 is phenyl, pyridyl, pyridazinyl, pyrimidinyl, furyl or thienyl.

8. A compound according to claim 7 wherein Ar_3 is substituted by C_{1-4}alkylsulfonylamino, fluoroC_{1-4}alkylsulfonylamino, C_{1-4}alkylcarbonylamino, fluoroC_{1-4}alkylcarbonylamino, halogen, nitrile, C_{1-4}perfluoroalkyl, C_{1-4}alkylcarbonyl, fluoroC_{1-4}alkylcarbonyl, aminocarbonyl, C_{1-4}alkylaminocarbonyl or di-C_{1-4}alkylaminocarbonyl.

9. A compound according to claim 1 wherein

Ar_1 is phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indolyl, benzofuranyl, benzothiophenyl or indazolyl; where Ar_1 is optionally substituted by 1-4 R^1 groups which may be the same or different;

Ar_2 is phenyl, pyridyl, thiazolyl, oxazolyl, pyrazolyl or imidazolyl; each of which is optionally substituted by 1-4 groups independently selected from the list: C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, aminoC_{1-4}alkyl, mono-C_{1-4}alkylaminoC_{1-4}alkyl, di-C_{1-4}alkylaminoC_{1-4}alkyl, $-O(CH_2)_nC(O)NR_xR_y$ and $-CO_2(CH_2)_pCH_3$;

Ar_3 is phenyl, pyridyl, pyridazinyl, pyrimidinyl, furyl or thienyl; wherein Ar_3 is optionally substituted by 1-4 groups independently selected from the group consisting of: C_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_3$, $-NHSO_2CH(CH_3)_2$), fluoroC_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_2CF_3$), C_{1-4}alkylcarbonylamino, fluoroC_{1-4}alkylcarbonylamino, halogen (such as chlorine), nitrile,

C_{1-4}perfluoroalkyl, C_{1-4}alkylcarbonyl, fluoroC_{1-4}alkylcarbonyl, aminocarbonyl, C_{1-4}alkylaminocarbonyl and di-C_{1-4}alkylaminocarbonyl;

E is n-butylene;

X is $-NR^aCO-$;

R^1 is halogen, C_{1-4}alkoxy or C_{1-4}alkyl;

R^a is C_{1-4}alkyl or hydrogen;

R_x and R_y are independently hydrogen or C_{1-4}alkyl;

n is 1-3; and

p is 0-3.

10. A compound according to claim 1 wherein

Ar_1 is phenyl, 1,2,3,4-tetrahydronaphthyl or indolyl; where Ar_1 is optionally substituted by 1-2 R^1 groups which may be the same or different;

Ar_2 is phenyl, pyridyl, thiazolyl, oxazolyl, pyrazolyl or imidazolyl; each of which is optionally substituted by 1-4 groups independently selected from the list: C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, aminoC_{1-4}alkyl, mono-C_{1-4}alkylaminoC_{1-4}alkyl, di-C_{1-4}alkylaminoC_{1-4}alkyl, $-O(CH_2)_nC(O)NR_xR_y$ and $-CO_2(CH_2)_pCH_3$;

Ar_3 is phenyl, pyridyl, pyridazinyl, pyrimidinyl or thienyl; wherein Ar_3 is optionally substituted by 1-4 groups independently selected from the group consisting of: C_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_3$, $-NHSO_2CH(CH_3)_2$), fluoroC_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_2CF_3$), C_{1-4}alkylcarbonylamino, fluoroC_{1-4}alkylcarbonylamino, halogen (such as chlorine), nitrile, C_{1-4}perfluoroalkyl, C_{1-4}alkylcarbonyl, fluoroC_{1-4}alkylcarbonyl, aminocarbonyl, C_{1-4}alkylaminocarbonyl and di-C_{1-4}alkylaminocarbonyl;

E is n-butylene;

X is –NHCO-;

R^1 is C_{1-4}alkoxy or C_{1-4}alkyl;

R_x and R_y are independently hydrogen or C_{1-4}alkyl;

n is 1-3; and

p is 0-3.

11. A compound according to claim 1 wherein

Ar_1 is phenyl, 1,2,3,4-tetrahydronaphthyl or indolyl; where Ar_1 is substituted by 1-2 R^1 groups which may be the same or different;

Ar_2 is phenyl, pyridyl, thiazolyl, oxazolyl, pyrazolyl or imidazolyl; each of which is optionally substituted by 1-4 groups independently selected from the list: hydroxy, hydroxyC_{1-4}alkyl, aminoC_{1-4}alkyl, mono-C_{1-4}alkylaminoC_{1-4}alkyl, di-C_{1-4}alkylaminoC_{1-4}alkyl, $-O(CH_2)_nC(O)NR_xR_y$ and $-CO_2(CH_2)_pCH_3$;

Ar_3 is phenyl, pyridyl, pyridazinyl, pyrimidinyl, furyl or thienyl; wherein Ar_3 is optionally substituted by 1-4 groups independently selected from the group consisting of: C_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_3$, $-NHSO_2CH(CH_3)_2$), fluoroC_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_2CF_3$), C_{1-4}alkylcarbonylamino, fluoroC_{1-4}alkylcarbonylamino, halogen (such as chlorine), nitrile, C_{1-4}perfluoroalkyl, C_{1-4}alkylcarbonyl, fluoroC_{1-4}alkylcarbonyl, aminocarbonyl, C_{1-4}alkylaminocarbonyl and di-C_{1-4}alkylaminocarbonyl;

E is n-butylene;

X is –NHCO-;

R^1 is C_{1-4}alkoxy or C_{1-4}alkyl;

R_x and R_y are independently hydrogen or C_{1-4}alkyl;

n is 1-3; and

p is 0-3.

12. A compound according to claim 1 wherein

Ar_1 is phenyl, 1,2,3,4-tetrahydronaphthyl or indolyl; where Ar_1 is optionally substituted by 1-2 R^1 groups which may be the same or different;

Ar_2 is pyridyl, oxazolyl, pyrazolyl or imidazolyl; each of which is optionally substituted by 1-4 groups independently selected from the list: C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, aminoC_{1-4}alkyl, mono-C_{1-4}alkylaminoC_{1-4}alkyl, di-C_{1-4}alkylaminoC_{1-4}alkyl, $-O(CH_2)_nC(O)NR_xR_y$ and $-CO_2(CH_2)_pCH_3$;

Ar_3 is phenyl, pyridyl, pyridazinyl, pyrimidinyl, furyl or thienyl; wherein Ar_3 is optionally substituted by 1-4 groups independently selected from the group consisting of: C_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_3$, $-NHSO_2CH(CH_3)_2$), fluoroC_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_2CF_3$), C_{1-4}alkylcarbonylamino, fluoroC_{1-4}alkylcarbonylamino, halogen (such as chlorine), nitrile, C_{1-4}perfluoroalkyl, C_{1-4}alkylcarbonyl, fluoroC_{1-4}alkylcarbonyl, aminocarbonyl, C_{1-4}alkylaminocarbonyl and di-C_{1-4}alkylaminocarbonyl;

E is n-butylene;
X is –NHCO-;
R^1 is C_{1-4}alkoxy or C_{1-4}alkyl;
R_x and R_y are independently hydrogen or C_{1-4}alkyl;
n is 1-3; and
p is 0-3.

13. A compound according to claim 1 wherein
Ar_1 is phenyl, 1,2,3,4-tetrahydronaphthyl or indolyl; where Ar_1 is optionally substituted by 1-2 R^1 groups which may be the same or different;
Ar_2 is phenyl, pyridyl, thiazolyl, oxazolyl, pyrazolyl or imidazolyl; each of which is optionally substituted by 1-4 groups independently selected from the list: C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, aminoC_{1-4}alkyl, mono-C_{1-4}alkylaminoC_{1-4}alkyl, di-C_{1-4}alkylaminoC_{1-4}alkyl, $-O(CH_2)_nC(O)NR_xR_y$ and $-CO_2(CH_2)_pCH_3$;
Ar_3 is phenyl, pyridyl, pyridazinyl, pyrimidinyl, furyl or thienyl; wherein Ar_3 is optionally substituted by 1-4 groups independently selected from the group consisting of: C_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_3$, $-NHSO_2CH(CH_3)_2$), fluoroC_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_2CF_3$), C_{1-4}alkylcarbonylamino, fluoroC_{1-4}alkylcarbonylamino, halogen (such as chlorine), nitrile, C_{1-4}perfluoroalkyl, C_{1-4}alkylcarbonyl, fluoroC_{1-4}alkylcarbonyl, aminocarbonyl, C_{1-4}alkylaminocarbonyl and di-C_{1-4}alkylaminocarbonyl;
E is n-butylene;
X is –NHCO-;
R^1 is C_{1-4}alkoxy or C_{1-4}alkyl;
R_x and R_y are independently hydrogen or C_{1-4}alkyl;
n is 1-3; and
p is 0-3.

14. A compound according to claim 1 wherein
Ar_1 is phenyl, 1,2,3,4-tetrahydronaphthyl or indolyl; where Ar_1 is optionally substituted by 1-2 R^1 groups which may be the same or different;
Ar_2 is phenyl, pyridyl, thiazolyl, oxazolyl, pyrazolyl or imidazolyl; each of which is optionally substituted by 1-4 groups independently selected from the list: C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl,

aminoC$_{1-4}$alkyl, mono-C$_{1-4}$alkylaminoC$_{1-4}$alkyl, di-C$_{1-4}$alkylaminoC$_{1-4}$alkyl, -O(CH$_2$)$_n$C(O)NR$_x$R$_y$ and -CO$_2$(CH$_2$)$_p$CH$_3$;

Ar$_3$ is pyridyl, pyridazinyl, pyrimidinyl, furyl or thienyl; wherein Ar$_3$ is optionally substituted by 1-4 groups independently selected from the group consisting of: C$_{1-4}$alkylsulfonylamino (such as -NHSO$_2$CH$_3$, -NHSO$_2$CH(CH$_3$)$_2$), fluoroC$_{1-4}$alkylsulfonylamino (such as -NHSO$_2$CH$_2$CF$_3$), C$_{1-4}$alkylcarbonylamino, fluoroC$_{1-4}$alkylcarbonylamino, C$_{1-4}$alkylcarbonyl, fluoroC$_{1-4}$alkylcarbonyl, aminocarbonyl, C$_{1-4}$alkylaminocarbonyl and di-C$_{1-4}$alkylaminocarbonyl;

E is n-butylene;

X is –NHCO-;

R^1 is C$_{1-4}$alkoxy or C$_{1-4}$alkyl;

R$_x$ and R$_y$ are independently hydrogen or C$_{1-4}$alkyl;

n is 1-3; and

p is 0-3.

15. A compound according to claim 1 selected from the list:

2-Hydroxymethyl-4'-trifluoromethyl-biphenyl-4-carboxylic acid {4-[4-(1H-indol-3-yl)-piperidin-1-yl]-butyl}-amide (Example 1);

2-(4-Cyano-phenyl)-4-hydroxymethyl-thiazole-5-carboxylic acid {4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-amide (Example 7);

2-(4-Chloro-phenyl)-4-hydroxymethyl-thiazole-5-carboxylic acid {4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-amide (Example 10);

5-(4-Cyano-phenyl)-2-(2-hydroxy-ethyl)-2H-pyrazole-3-carboxylic acid {4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-amide (Example 21);

4-(5-Chloro-thiophen-2-yl)-N-{4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-benzamide (Example 23);

4-(5-Chloro-pyridin-2-yl)-N-{4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-benzamide (Example 32);

4-(6-Chloro-pyridin-3-yl)-N-{4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-benzamide (Example 34);

6-(4-Chloro-phenyl)-N-{4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-nicotinamide (Example 38);

6-(4-Cyano-phenyl)-N-{4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-nicotinamide (Example 39);

6-(5-Chloro-thiophen-2-yl)-N-{4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-nicotinamide (Example 40); and

2-(4-chlorophenyl)-1,4-dimethyl-1H-imidazole-5-carboxylic acid {4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-amide (Example 45).

16. A pharmaceutical composition comprising a compound as defined in any preceding claim and a pharmaceutically acceptable carrier or diluent.

17. The use of a compound defined in any one of claims 1 to 15 in the manufacture of a medicament for use in the treatment of conditions resulting from elevated circulating levels of LDL-cholesterol.

18. A compound defined in any one of claims 1 to 15 for use as a medicament.